A RESEARCH PROPOSAL

‘‘QbD BASED DESIGN AND DEVELOPMENT OF ORAL HERBAL ANTIDIABETIC FORMULATION’’

Submitted

For the consideration of registration for the degree of

DOCTOR OF PHILOSOPHY

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1. INTRODUCTION

Diabetes can be considered as a major public health and economic problem across the globe. According to the International Diabetes Federation (IDF) the currently, 537 million adults are estimated to be suffering from diabetes. The total number of people living with diabetes is projected to rise to 643 million by 2030 and 783 million by 2045. Almost 1 in 2 (240 million) adults living with diabetes are undiagnosed. Diabetes caused 6.7 million deaths. These data show that the number of patients with diabetes is increasing at an alarming rate and have come to represent a challenge for human health.[1]

Diabetes mellitus commonly referred to as diabetes, is a group of metabolic disorders in which high blood sugar levels occur over a prolonged period. Diabetes mellitus is divided into two main categories: type 1 DM (T1DM), an autoimmune disease associated with insulin deficiency, and type 2 DM (T2DM), which occurs mainly due to ineffective insulin action. Typical Diabetes mellitus patients exhibit frequent urination, increased thirst, increased hunger, and other symptoms.

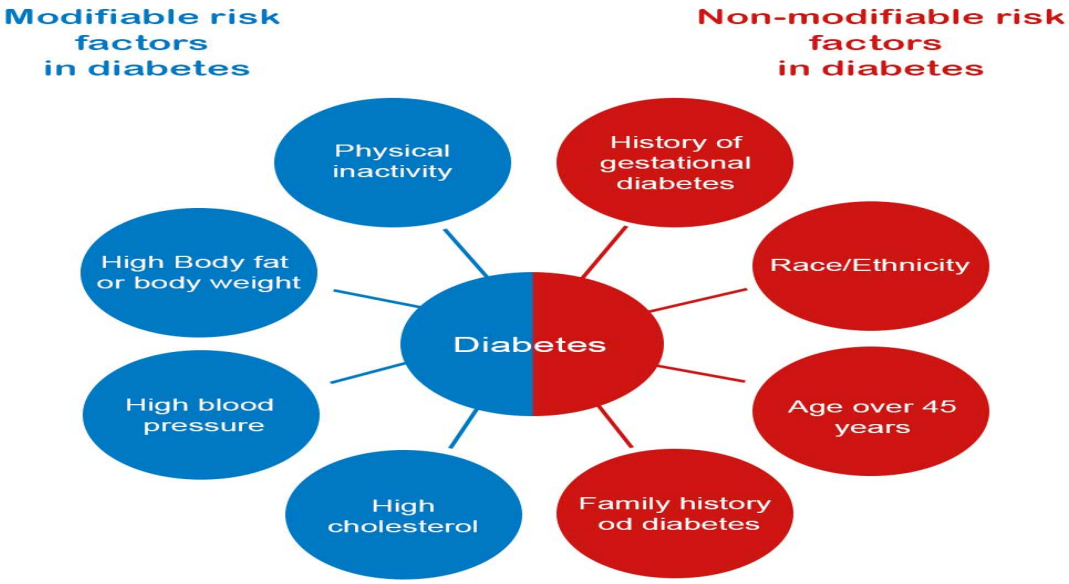

Fig.1 Risk factors of diabetes

Diabetes is treated mainly with oral hypoglycemic drugs and insulin injection. Western medical treatment methods for diabetes include injection of hypoglycemic agents (insulin, insulin analogs, etc.) and oral administration of synthetic hypoglycemic drugs, such as sulfonyl ureas, biguanides, glinides, glycosidase inhibitors and thiazolidinedione derivatives. However, all of these medications have specific toxic side effects, and long-term use of insulin causes decreased insulin receptor sensitivity, resulting in insulin resistance and eventually leading to worsening of control conditions. As a result, an increasing amount of research is focused on the development of safer and more economical hypoglycemic drugs. Also the more importance is in herbal medication due to safety and efficacy. [2, 3]

Examples of synthetic drugs and their side effects: [4]

Sr. No.	Name of antidiabetic drug	Side effects
01	Insulin	Allergic reactions at injection site
02	Sulfonylurea	Hypoglycemia
03	Thiazolidinedione	Swelling due to water retention, weight gain
04	Meglitinides	Hypoglycemia
05	Biguanide	Diarrhea, metallic aftertaste, nausea
06	alpha-glucosidase inhibitors	Bloating, flatulence
07	Dipeptidyl- peptidase-4 inhibitors	Pharyngitis, headache
08	Glucagon-like peptide-1 agonist	Diarrhea, nausea, vomiting
09	Sodium glucose cotransporter 2 inhibitors	Genital and urinary infections, more frequent urination
10	Dopamine agonists	Nausea, hypotension, and orthostatic hypotension
11	Metformin	Heart failure, Liver disease

Numbers of studies are done on herbal medication of antidiabetic treatment. Our Vedic literatures like Charak Samhita already report the use of plants, herbs and their derivatives for treatment of diabetes mellitus. More than 400 plants have been incorporated in approximately 700 recipes which are used to treat diabetes mellitus in almost two thirds of the world population. Examples of some antidiabetic drugs are Allium sativum, Catharanthus roseus, Ephedra distachya, Gymnema sylvestre, Psidium guajava L., Nelumbo nucifera Gaertn etc. [5,6]

Introduction to QbD

Quality by Design (QbD) is defined as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.[7] The Quality related guidelines such as the "Systems and Risk based approaches to cGMPs" revealed new key words for industry introducing the concepts of QbD, Quality Risk Management (QRM), Pharmaceutical Quality Systems (PQS) etc. [8]

Quality by Design (QbD) concept was first developed by Dr. Joseph M. Juran. His belief was that quality is something that has to be designed into a product and that the method of designing a product is responsible for most of the crises and problems associated with quality. The International Conference on Harmonization (ICH) now called Harmonization for Better Health has issued four guidelines i.e. ICH Q8 (R2), Q9, Q10, Q11 and Implementation documents that provide a general framework for the application of QbD to drug product and drug substance development and manufacture. In particular, ICH Q8 (R2) (issued in 2005 and revised in 2009) outlines and defines the main elements of the QbD framework. QbD tools facilitate a higher level of process understanding, root cause investigation [9]

Advantages of QbD[9]

1. QbD is helpful for the conceptual understanding based on Product design goal, Process Design space, Control space and Operating space.
2. QbD, a regulatory-driven approach emphasizes on product as well as process control for systematic product development based on predefined goals and quality risk management.
3. Major safety and efficacy of various drug delivery systems can be ensured by the optimal use of QbD.
4. QbD tools facilitate a higher level of process understanding, root cause investigation and developing control strategies in the process and formulation development.
5. Science based understanding of the process results in minimized batch failure or rework along with better consistency and efficacy.

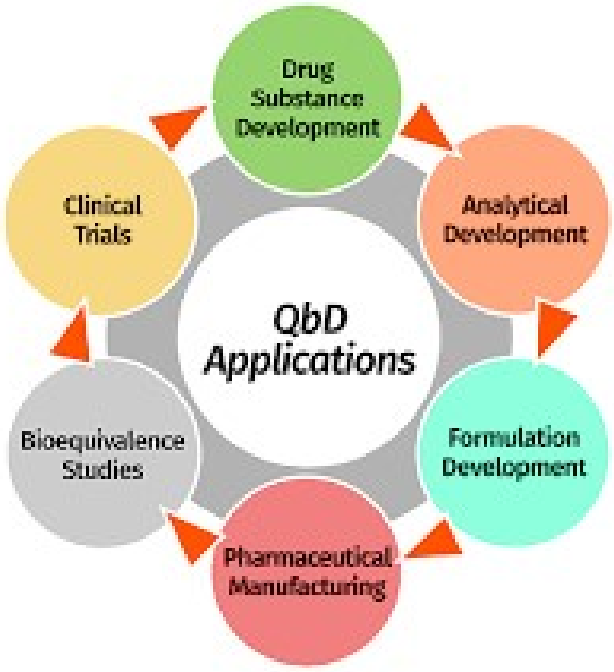

Fig.2 Applications of QbD in Pharmaceutical

2. REVIEW OF LITERATURE

Ali S. Alqahtani et.al. (2022) summarized the available antidiabetic medicinal plants in the Kingdom of Saudi Arabia with its phytoconstituents and toxicological findings. The selected plant species *H. salicornicum, T. oliverianum, A. cepa, A. herba-alba, Teucrium polium, Sesamum indicum, Z. spina-christi,* and F. religiosa are the native Saudi medicinal plants traditionally used for the treatment of DM . This data showed that 20 medicinal plants are traditionally used in Tabuk region of Saudi Arabia which were potent antidiabetic.[10]

Wensink MJ, et.al. (2022) evaluated whether the risk of birth defects in offspring varies with preconceptional pharmacologic treatment of fathers with diabetes using cohort study. They found that the preconception paternal metformin treatment is associated with major birth defects, particularly genital birth defects in boys.[11]

Fahadul Islam , et.al. (2022) studied neuro pharmacological and antidiabetic properties of *Lannea coromandelicaleaves* extracts in animal models. The extracts of *L. coromandelica* hold significant neuro-modulatory properties. The leaves extract had no significant effect on normal blood sugar levels, but they did effectively correct alloxan-induced alterations in blood sugar and pancreatic beta-cell population. Hence the study of this plant for anti-diabetic activity can be the future goal.[12]

Waleed Y. Rizg et.al. (2022) had studied antidiabetic activity of glibenclamide microspheres by QbD. The study concluded that the penetration and absorbance of glibenclamide was enhanced using S-protected thiolated okra polymer. This showed the use of herbal content as a polymer in antidiabetic formulation. Also the DoE was central composite design used to optimize glibenclamide microspheres. [13]

Vishakha Parab Gaonkar et.al. (2020) performed standardization of antidiabetic *Trigonella foenum-graecum L.* seeds by using QbD based HPLC method. The present research work was a successful example of the implementation of QbD concept for marker based standardization of herbal drug along with the evaluation of important quality control parameters.[14]

Naseem Akhtar et.al. (2020) glanced at the self-generating nano-emulsification techniques for anti-cancers and anti-diabetics drugs of natural and synthetic origins with quality by design approach. The drugs administered through the oral route with unfavorable solubility, erratic release profile, lowered bioavailability characteristics have been effectively formulated using SNEDDS.[15]

Francesca Pivari et.al. (2019) had reviewed on curcumin and concluded that it has therapeutic potential to counteract diabetes and its complications. The doses of upto 12 g per day of curcumin are safe, tolerable and non-toxic.[16]

JamesFlory et.al. (2019) had focused on metformin, a drug of herbal origin that has been widely used to treat diabetes. Metformin remains a good first-line pharmacologic treatment for type2 diabetes in most patients. Adverse effects are common but may be mitigated by careful dose titration, good communication with patients, and use of extended-release formulations.[17]

MA Shah (2019) worked on RP-HPLC method development and validation for estimation of Gallic acid, Ellagic acid and Curcumin using DAD as a detector. For method development QbD approach was incorporated using CCD (Central composite Design) approach as Experimental Design. Also HPTLC method for simultaneous estimation of Gallic acid, Ellagic acid and Curcumin in Polyherbal Antidiabetic formulations was developed which is important tool in standardization of Herbal Medical product in initial stage of Research.[18]

Habib Yaribeygi et.al. (2018) had reviewed on Antidiabetic potential of saffron and its active constituents and they conclude that saffron is a safe and efficacious natural product that might serve as an adjunct to routine antidiabetic medications.[19]

Vijay Mishra et.al. (2018) reviewed Quality by design approaches in current pharmaceutical set-up. The data showed different QbD designs and parameters for different formulations.[20]

Jiaxiang Zhanga et.al. (2018) have prepared amorphous Ibuprofen filaments successfully via the Hot melt extrusion method process and found acceptable for FDM 3D printability. In addition, all 15 batches of tablets with different designs according to Box-Behnken approach were successfully. It showed the importance and applicability of QbD in oral formulation.[21]

Stavros N. Politis et.al. (2018) reported the DoE in pharmaceutical development. The data revealed the area of formulation and suitable DoE for it. For oral formulations Multivariate design (fractional factorial design in 14 variables, 35 experiments), Fractional factorial designs, Mixture design are considerable for use.[8]

Ruba Ismail et.al. (2017) had reviewed on "Novel strategies in the oral delivery of antidiabetic peptide drugs- insulin, GLP 1 and its analogs". It summarized that drugs like insulin, GLP-1 and its analogs are still delivered parenterally due to numerous potential physiochemical and enzymatic barriers that limit their absorption in the GI tract. Because of its several advantageous properties, many attempts have been made to achieve oral delivery of these peptides using various strategies. Despite these significant research efforts in this field, there is still no FDA approved oral insulin or Glp-1 analog on the market.[22]

Kanwal Firdous et.al. (2016) had studied a comparative role of oral and parenteral anti-diabetic agents in diabetic patients with acute myocardial infarction. They found that patients of diabetes

mellitus have more possibilities for acute myocardial infarction as compared to that of the patients without diabetes.[23]

José Luis Ríos et.al. (2015) reviewd number of natural plant products for the treatment of type 2 dibetes mellitus. They summarized that Picnogenol, acarbose, miglitol, and voglibose as potent antidiabetic products of natural origin along with their mechanism of action.[24]

Voluminous literature survey reveals that in traditional treatments so many herbal plants are used for diabetes. The survey showed the impact of herbal medication in diabetes over synthetic due to their safety and efficacy. But some herbal medications are hidden from pharmaceutical sector because of unexamined activity of plants and their formulation problems. Hence this study is proposed to glance on such potent herbal medicinal plants that are useful for antidiabetic activity. Also the survey evinced the QbD platform for herbal formulations. Hence accordingly the study is planned to perform using this new design tool in herbal formulation.

Antidiabetic plant profiles:

Sr. No	Name of plant	Family	Antidiabetic constituents
01	Aegle marmelos	Rutaceae	Aegeline
02	Embelia ribes	Myrsinaceae	Embelin
03	Allium sativum	Liliaceae	Allicin
04	Catharanthus roseus	Apocynaceae	Vindoline, vindolinine
05	Ephedra distachya	Ephedraceae	l-ephedrine
06	Gymnema sylvestre	Asclepiadaceae	Gymnemic acids
07	Momordica charantia	Cucurbitaceae	Charantin
08	Psidium guajava L.	Myrtaceae	Triterpenoid
09	Nelumbo nucifera Gaertn	Nymphaeaceae	Tryptophan
10	Rhizoma Pinelliae	Areaceae	Flavone C-glycoside

Pharmaceutical QbD designs and tools

1. Plackett-Burman (PB) design 2. Central composite design 3. Face centered design

4. Box-Behken design 5. Star designs 6. Mixture designs 7. Taguchi designs 8. Optimal designs

In view of above, present study is envisaged to screen any above or other potent medicinal plant/plants for its effectiveness in Diabetes Mellitus and formulate it in oral dosage form by using any above or any other suitable QbD design.

3. OBJECTIVE

- To formulate, evaluate and optimize oral herbal formulation using selected herbal drug/drugs and excipients by Quality by design.
- T o identify antidiabetic activity of prepared oral herbal formulation.
- To study the prepared formulation for preclinical evaluations, in-vivo and in-vitro release.

4. HYPOTHESIS

- By taking idea from literature review we are decided to work on the preparation of oral herbal antidiabetic formulation by using QbD approach.
- Due to long term treatment of diabetes, the herbal medicinal therapy can be the best alternative over synthetic drugs to minimize the occurrence of side effects.
- In the traditional treatment many plants are used for antidiabetic activity but some of them are away from pharmaceutical segment due to their formulation problems.
- The purpose of the study is to examine such potent medicinal plant/plants and creating pharmaceutical formulations by overcoming the all problems which will be helpful in the management of diabetes.

5. METHODOLOGY

1. Collection and Authentication of plant/plants: The whole plant/plants or its parts will be collected from the known sources. The sample will get identify and authenticate by the botanist of region.

2. Processing of plant material: Collected plant/plants material will be subjected to processing such as drying, grinding, sieving etc as per official standards.

3. Extraction of plant/plants material: Coarse powder form of plant material will be subjected to successive extraction. The solvent & extraction method will be decided according to chemical constituents & its nature.

4. Preliminary phytochemical tests and pharmacological evaluation of extract/extracts

5. Selection of excipients according to drugs

6. Compatibility studies

7. Pre-formulation studies

8. Formulation & Development of oral formulation by QbD

9. Evaluation of formulated product by preclinical study, in-vivo and in-vitro release

10. Optimization of formulation: The one of the designs of QbD will be applied to the observed evaluation parameters for optimization process.

11. Statistical Analysis, Data Interpretation and Conclusions.

6. IMPORTANCE OF STUDY

- Now a day's people are demanding natural products than synthetic due to its higher safety and efficacy window.
- The present study will be based on such herbal medicinal plants having formulation problems and due to this they afield of pharmaceutical formulation focus.
- The present study will also indicate the importance of QbD approach and its implementation in the preparation and optimization of herbal formulation product.
- The importance of study is to improve patient compliance and enhance effectiveness of treatment by formulating oral herbal antidiabetic formulation.

7. DURATION OF WORK

Sr.No.	Work	Period
1.	Literature survey	6months
2.	Collection of plant materials	2months
3.	Extraction of plant materials	4months
4.	Phytochemical study	3months
5.	Pre-formulation study	1months
6.	Formulation & Development using QbD	6months
7.	Evaluation of formulated product by Preclinical study , in-vivo and in-vitro release	11months
8.	Other suggested work and compilation of data	3months
	Total duration of work	36month

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